

Guidance for Industry and for FDA Reviewers

**Refractive Implants: Guidance for  
Investigational Device Exemptions  
(IDE) and Premarket Approval  
(PMA) Applications; Draft**

*Draft Guidance – Not for Implementation*

**This guidance document is being distributed for comment purposes only.  
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Food and Drug Administration  
Center for Devices and Radiological Health**

**Intraocular and Corneal Implants Branch  
Division of Ophthalmic and ENT Devices  
Office of Device Evaluation**

# Preface

## **Public Comment:**

For 90 days following the date of publication in the Federal Register of the notice announcing the availability of this guidance, comments and suggestions regarding this document should be submitted to the Docket No. assigned to that notice, Dockets Management Branch, Division of Management Systems and Policy, Office of Human Resources and Management Services, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD 20852.

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# Refractive Implants: Guidance<sup>1</sup> for Investigational Device Exemptions (IDE) and Premarket Approval (PMA) Applications

## I. Introduction

- A. **Scope** - This guidance document applies to any ocular implant whose primary indication is the modification of the refractive power of a phakic eye to improve distance and/or near uncorrected visual acuity. This document also applies to any intraocular lens (IOL) intended for clear lens exchange.

Note: Sponsors who pursue clear lens exchange as a refractive indication should be aware that FDA may recommend additional safety and efficacy endpoints. Sponsors interested in pursuing this indication should contact the Intraocular and Corneal Implants Branch for additional information.

- B. **Definitions** - The following definitions apply:

### General

**refractive implant (RI)** - device, implanted in the eye, for which the primary indication is the modification of the refractive power of a phakic eye to improve distance and/or near uncorrected visual acuity; also intraocular lenses intended for clear lens exchange

**intraocular RI** - RI placed in the anterior or posterior chamber

**intracorneal RI** - RI placed within the cornea

**finished device lot** - all units of an RI that have undergone a single series of manufacturing operations including the sterilization operation, and that are identified on a single device history record

### Optical

**body** - for an RI resembling an intraocular lens (IOL), the central part of the implant incorporating the optic

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<sup>1</sup>This document is intended to provide guidance. It represents the Agency's current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

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**clear optic** -for an RI resembling an IOL, the diameter of the circle, concentric with the optical axis of the RI, containing only features of the RI belonging to the optical design

**haptic** - non-optical, generally peripheral, component(s) of an RI intended to keep it in place in the eye

***in situ*** - in equilibrium with aqueous humor at 35°C.

Note 1: The refractive index of aqueous humor is taken to be 1.336 at 546.07 nm.

Note 2: For practical testing purposes, physiological saline may in many cases be used as a substitute for aqueous humor.

Note 3: Actual testing may be carried out at other conditions if, by validated correction procedures, values can be shown to apply under *in situ* conditions.

**loop** - peripheral extension on the body, serving to position the RI in the eye

Note: Loops are parts of the haptic, or may be the haptic.

**optic** - image-forming, generally central, component of an RI

**overall diameter** - for an RI resembling an IOL, the diameter of the cylinder circumscribing an RI with the axis of the cylinder coincident with the optical axis of the RI

**dioptric power** - reciprocal of the reduced paraxial focal length *in situ* for light with a wavelength of 546.07 nm; expressed in diopters (D)

**paraxial focal length** - distance between the back principal plane and the back paraxial focal point

**reduced focal length** - focal length divided by the refractive index of the surrounding medium

### Physical and mechanical

**optic decentration** - lateral displacement of the optic due to compression of the haptic(s), measured as distance between the geometric center of the clear optic and the center of a cylinder of a specified diameter to which the RI is confined

**optic tilt** - angle between the optical axis of the RI in the uncompressed state and that in the compressed state, with the RI being confined to a specified diameter

**sagitta** - maximum distance between the planes, normal to the optical axis, which contact respectively the most anterior and most posterior points, be it haptic or optic, of an uncompressed RI

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**vault height** - distance between the plane, normal to the optical axis, containing the vertex of the iris-proximal optical surface and the plane, normal to the optical axis, containing the most iris-proximal point of the uncompressed haptic of an RI

Note 1: The iris-proximal side of the RI refers to the intended position as implanted.

Note 2: The vault height is positive if the distance defined is in the direction towards the retina as implanted, and negative if not.

### Biocompatibility

**non-ocular implantation test** - test that evaluates the local toxicity and irritation of a test material on non-ocular tissue, using an appropriate implant site in an animal at both the gross and the microscopic level

**ocular implantation test** - test that evaluates the reciprocal tolerance of the test material and ocular tissue at both the gross level and the microscopic level when the test material is surgically implanted into the intended placement site in the eye of an appropriate model

**test material** - either the finished RI, as intended for human implantation, or facsimile material manufactured and processed in a validated procedure equivalent to that used for the RI

**photostability test** - test that determines the potential for degradation of a test material due to exposure to light

### **Labeling and packaging**

**primary package** - container that physically and directly protects the RI and that may maintain sterility

**self-adhesive label** - label included in the storage container for hospital record use

**storage container** - packaging intended to protect the device during storage and distribution

**expiration date** - date of termination of shelf-life, after which the RI is not to be used

**package integrity** - container's ability to protect the RI from contamination

**shelf-life** - period during which an RI remains suitable for implantation in the human eye

**stability** - extent to which a product retains properties and characteristics within the manufacturer's specified limits, throughout its period of storage, i.e., its shelf-life

### Clinical

**lost to follow-up** - total number of subjects for whom a visit at the prescribed postoperative visit or later has not been obtained but are not considered to be active or discontinued

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**BSCVA** - best spectacle-corrected visual acuity

**UCVA** - uncorrected visual acuity

**MRSE** - manifest refraction spherical equivalent

**serious adverse event** - In addition to the definition of adverse event in ISO 14155, an adverse event that is potentially sight-threatening is a serious adverse event. This is consistent with the definition of serious adverse event on FDA Form 3500 that is used for reporting serious adverse events and product problems with human drug and biologic products and devices (FR Vol. 58, No. 105, pp. 31596-31614).

**unanticipated adverse device effect** - any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of patients (see 21 CFR 812.3(s)).

**persistent adverse event** - an adverse event that is present at the conclusion of a clinical investigation

**cumulative adverse event** - total number of adverse events that have occurred at any time up to a specified point in time postoperatively

### **C. Abbreviations**

**AC** - angle of contact

**ANSI** - American National Standards Institute

**ASTM** - American Society for Testing and Materials

**D** - diopter

**DIS** - draft international standard

**ECH** - ethylene chlorohydrin

**EO** - ethylene oxide

**IOL** - intraocular lens

**IDE** - investigational device exemption

**ISO** - International Organization for Standardization

**LFB** - lower force boundary

**MEM** - minimum essential medium

**MTF** - modulation transfer function

**PDP** - product development protocol

**PMA** - premarket approval application

**PMMA** - polymethylmethacrylate

**RI** - refractive implant

**T<sub>a</sub>** - temperature used in accelerated study

**T<sub>o</sub>** - typical storage temperature

**UFB** - upper force boundary

**USP** - United States Pharmacopeia

## **II. Biocompatibility Testing**

### **A. General**

Tests should be conducted on the finished product as marketed, or on material that has undergone the same manufacturing and sterilization processes as the RIs. The test methods specified below are suggested methods. Alternative methods are permitted if appropriately validated. The omission of certain tests should be justified with a valid scientific argument/rationale.

### **B. Extracts**

In tests that are conducted on material extracts, testing should be conducted with two different extractants, one of which is an aqueous solution, e.g., physiological saline (sponsor should define formulation), and the other a lipophilic or dipolar solvent, under conditions as described in ISO/FDIS 11979-5, Annex A. See USP 24, <88>, 2000, for examples of acceptable extractants.

Extraction for cytotoxicity testing is an exception that should be performed according to ISO 10993-5, Test for Cytotoxicity, In Vitro Methods. The extractant(s) used shall be appropriate for the cytotoxicity test protocol(s).

### **C. Biocompatibility Tests**

For refractive implant materials, all biocompatibility tests listed below should be performed.

#### **1. Cytotoxicity -**

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Cytotoxicity testing should be carried out in accordance with the requirements of ISO 10993-5.

All of the following cytotoxicity tests are recommended to be performed:

<u>Test</u>	<u>Desired Result</u>
Agar Diffusion Test (Direct Contact)	Non-cytotoxic
Agar Diffusion Test (Extracts)	Non-cytotoxic
Inhibition of Cell Growth	Non-inhibitory
MEM Elution	Non-cytotoxic

Sponsors should provide a scientific rationale for the exclusion of any of the tests.

### 2. Genotoxicity -

Testing for genotoxic potential should be conducted using two extractants as outlined in Annex A, in accordance with ISO 10993-3.

The results should show the material to be non-genotoxic. Otherwise, additional genotoxicity and/or carcinogenicity testing will be necessary.

### 3. Maximization Sensitization Test -

Testing for sensitization potential is to be conducted as outlined using two extractants as outlined in Annex B, in accordance with ISO 10993-10.

The results should demonstrate a lack of sensitization potential.

### 4. Non-Ocular Animal Implantation Test -

This test is performed in order to demonstrate the tissue tolerance of the test material. Testing is to be conducted in accordance with Annex C.

The results should demonstrate tolerance of the tissue material.

### 5. Ocular Implantation Test -

This test is performed in order to demonstrate the tolerance of the test material after implantation into the animal eye.

The results should demonstrate that the test material is well tolerated by the ocular tissue and that the test material is stable over the implantation period.

FDA will consider requests for waivers from the ocular implantation test, provided that:

- a. the sponsor provides a valid scientific rationale for omitting the test;
- b. the material is chemically identical to a material that has been proven safe and effective as an implant in the human eye (e.g., certain polymethylmethacrylates (PMMA's)); and,
- c. the material is derived from the same source as a material proven safe and

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effective as an implant in the human eye.

Note: Scanning Electron Micrographs (SEMs) should be performed at the end of the animal study. However, if the physical properties of the material make it impossible to obtain SEMs because the material is gelatinous, the sponsor should provide an explanation.

### 6. Test of Extractables and Hydrolytic Stability

Testing should be conducted as outlined in Annex A of ISO 11979-5.

### 7. Test of Extractables by Exhaustive Extraction -

Exhaustive extraction in an appropriate solvent should be performed to swell the polymer for determination of absolute levels of any free monomers, UV absorber or contaminants. A suggested method for implants made of PMMA may be found in Annex A of ANSI Z80.7 IOL Standard (1994) or Annex B of ISO/DIS2 11979-6.

### 8. Test for Photostability -

Testing should be conducted as outlined in Annex B of ISO 11979-5, except that the light intensity value should be adjusted to  $0.75 \text{ mW/cm}^2$  for corneal RIs (the adjusted value takes into account the different position of the implant in the eye).

### III. Optical Testing

#### A. General

The recommended tests should be performed on the finished product as marketed, unless otherwise specified. The following recommendations apply to refractive implants that are intended to function optically.

#### B. Dioptric power

When determined by one of the methods described or referenced in Annex A of ISO 11979-2, the spherical dioptric power of a RI should be within the following tolerance limits in all meridians:

<b>Nominal dioptric power range</b>	<b>Tolerance on dioptric power (D)</b>
0 to $\leq$ 15	$\pm 0.3$
$>$ 15 to $\leq$ 25	$\pm 0.4$
$>$ 25 to $\leq$ 30	$\pm 0.5$
$>$ 30	$\pm 1.0$

Note 1: For spherical RIs, astigmatism is implicitly limited by the requirement that dioptric power be within the tolerance limits of Table 1 in all meridians. The demand on imaging quality (see III.C below) also prevents excessive astigmatism.

Note 2: The tolerances listed in Table 1 represent the combined manufacturing and measurement tolerances around the nominal power. Manufacturers should set their manufacturing tolerances tighter than those listed in Table 1 to meet this combined tolerance.

Note 3: The ranges listed in Table 1 apply to positive as well as negative dioptric powers.

The cylindrical dioptric power of a RI shall be within the following tolerance limits in the intended meridian:

<b>Nominal cylindrical power range (D)</b>	<b>Tolerance on cylinder (D)</b>
0 to $\leq$ 2	$\pm 0.25$
$>$ 2 to $\leq$ 4	$\pm 0.37$
$>$ 4	$\pm 0.5$

Note: The tolerances listed in Table 2 represent the combined manufacturing and measurement tolerances around the nominal power. Manufacturers should set their manufacturing tolerances tighter than those listed in Table 2 to meet this combined tolerance.

The cylindrical meridian shall be within the following tolerance limits:

**Table 3 - Tolerances on cylindrical meridian**

<b>Nominal cylindrical power range (D)</b>	<b>Tolerance on cylindrical meridian (°)</b>
0 to $\leq 1.50$	$\pm 5$
$>1.50$	$\pm 3$

**C. Imaging quality**

The resolution efficiency of a refractive implant with a spherical optic should be no less than 60% of the diffraction limited cut-off spatial frequency when determined in air according to the methods established in Annex B of ISO 11979-2. In addition, the image should have minimal aberrations other than normal spherical aberration.

Alternatively, the resolution efficiency may be evaluated with the lens in a wet cell as described in Section 6.2.3 of ANSI Z80.7. Under these conditions, the resolution efficiency should exceed 70% of the diffraction limited cut-off spatial frequency.

For those RIs for which the methods described above are not appropriate, imaging quality may be evaluated by modular transfer function (MTF) testing. The RI (in isolation) should exhibit an MTF value greater than 70% of the calculated maximum attainable for the design.

In addition, the image shall have minimal aberrations other than normal spherical aberration.

Note 1: The sponsor should demonstrate that the entire range of available powers of a refractive implant meets this specification.

Note 2: For RIs with cylindrical power, sponsors should evaluate the imaging quality and provide a description of the method used. Sponsors should also provide the results of a validation to demonstrate the accuracy and repeatability of the method. A specification for imaging quality should be established and a justification should be provided.

**D. Spectral Transmittance**

The spectral transmittance in the range 300 nm to 1200 nm should be recorded for the refractive implants of powers representing the thickest and thinnest optic. The spectrum should be recorded with a spectrophotometer with a band-width of not more than 5 nm and be accurate to  $\pm 2\%$  transmittance.

The spectrum should be recorded using sample refractive implants or flat pieces of the implant material having average thicknesses equal to that of the central 3 mm of the thickest and thinnest optics and that have undergone the same production treatment as the finished product, including sterilization. Refractive implants made of materials that change transmittance properties *in situ* should be measured with the implant under simulated *in situ* conditions. Additional information may be found in ISO 8599 and ISO 11979-2.

#### **IV. Dimensional Tolerances, Mechanical Characterization and Testing**

##### **A. General**

RIs whose dimensions are not appreciably affected by the temperature and aqueous environment *in situ* (e.g., PMMA products) should be evaluated at a documented controlled temperature and relative humidity. For all other devices, properties should be determined at *in situ* conditions with the temperature tolerance of  $\pm 2^{\circ}\text{C}$ . The precise composition of the solution used should be reported in all cases.

##### **B. Dimensions**

Tolerances for RIs to be placed in the anterior chamber should be established in accordance with ISO 11979-3. Manufacturers of other RI designs should establish tolerances for the following dimensions (where applicable) as validated through the clinical study. Once established, tolerances should be specified in the manufacturer's design documentation. The manufacturer should validate that production meets these tolerances to appropriate statistical levels.

The sponsor should evaluate the design of the implant in considering the establishment of additional manufacturing tolerances.

- Overall diameter

Note: For symmetrically designed devices with two haptics, the overall diameter equals the distance between haptic vertices.

- Vault height
- Sagitta
- Optic diameter
- Body dimensions

Note: For ellipsoid bodies, the dimensions of the body should be reported as (short axis) x (long axis).

- Thickness of the optic and haptics

##### **C. Mechanical Characterization**

The tests described below should be used to characterize the mechanical characteristics associated with a sponsor's design. They should be used during the initial design validation for a device model and to determine whether clinical requirements are necessary for modifications of that design.

###### **1. Clearance analysis**

An analysis of the optic clearance should be performed to determine the position of both the anterior and posterior surfaces of the device at its minimum recommended overall diameter in relation to the structures of the eye, as follows:

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- For RIs intended for placement in the anterior chamber, clearance of the anterior surface from the corneal endothelial layer in an eye with EITHER the minimum anterior chamber depth specified in the inclusion criteria and labeling, OR in a worst-case myopic or hyperopic eye where the worst-case situation is determined from the available power range and the indications for use.
- For RIs intended for placement in the posterior chamber, an analysis of clearance of the posterior surface from the crystalline lens should be performed.
- For all intraocular RIs, clearance of the closest RI surface from the iris in a worst-case eye, where the worst-case situation is determined from the available power range and the indications for use.

### **2. Clear optic diameter**

The clear optic diameter, as defined in section I.B, should be reported.

### **3. Compression force**

The compression force should be measured for all intraocular RIs with haptics. For RIs intended for placement in the anterior chamber, measurements should be made at the minimum and maximum intended compressed diameters as recommended by the manufacturer in the package insert. For all other RIs with haptics, the diameter(s) at which compression force is measured and a rationale for its use should be provided.

Note: A suggested method for compression force testing is described in ISO 11979-3 Annex A.

### **4. Compression force decay**

For all intraocular RIs with haptics, the compression force decay should be measured at the same diameters that were used for the testing described in C.3, after 24 hours in compression at each diameter under in situ conditions.

Note: A suggested method for compression force decay testing is described in ISO 11979-3 Annex F.

### **5. Axial displacement in compression**

For RIs with haptics intended for placement in the anterior chamber, the vault height and the sagitta in the compressed state at the minimum and maximum intended compressed diameters should be reported for both the dioptric powers at which the edge and center sagitta are the greatest. For all other intraocular RIs with haptics, the axial displacement in compression should be measured and reported at the same diameters that were used for the testing described in C.3.

Note: A suggested method for axial displacement in compression testing is described in ISO 11979-3 Annex B.

## **6. Angle of contact**

For RIs with haptics, the angle of contact (an approximation of the total haptic contact with the supporting ocular tissue) should be measured at the same diameters that were used for the measurement of compression force.

Note: A suggested method for angle of contact in compression testing is described in ISO 11979-3 Annex E.

### **D. Mechanical Testing**

Mechanical testing recommendations given below should be specified in the manufacturer's design documentation. The sponsor should validate that their production meets these tolerances. If dioptric power and/or dimension affect the property tested, lots covering the range of powers or dimensions should be used. The minimum sample size for each test should be 10 devices per lot per power/ dimension. The lots should be representative of finished devices being marketed. Testing should be performed on finished product (i.e., after sterilization/aeration), except for the bulk mechanical properties, which may be performed on material samples that have been processed through all steps of the manufacturing (including sterilization/aeration).

For RIs with haptics intended for placement in the anterior chamber, the requirements of ISO 11979-3 apply.

For all other RIs, the following testing should be performed, as described below.

#### **1. Optic decentration**

For RIs with haptics, optic decentration should be measured at the diameters used for compression testing. A specification for the maximum allowable decentration should be established, taking into consideration the effect of decentration on optical performance and clearance of anatomical structures.

Note: A suggested method for decentration testing is described in ISO 11979-3 Annex C.

#### **2. Optic tilt**

For RIs with haptics, optic tilt should be measured at the diameters used for compression testing. A specification for the maximum allowable tilt should be established, taking into consideration the effect of decentration on optical performance and clearance of anatomical structures.

Note: A suggested method for decentration testing is described in ISO 11979-3 Annex D.

#### **3. Loop strength**

For RIs with haptics, all loops should be able to withstand a force of 0.25 N before becoming detached from the optic.

Note: A suggested method for loop pull strength testing is described in ISO 11979-3 Annex H.

#### **4. Dynamic fatigue durability**

All flexible supports should be capable of withstanding, without being severely damaged or breaking, 250,000 cycles of near-sinusoidal deformation of  $\pm 0.25$  mm at a frequency between 1 Hz and 10 Hz according to the conditions described below:

- for posterior chamber RIs, around a compressed distance of 5.0 mm between the testing plate and the center of the optic
- for anterior chamber RIs, around a compressed distance corresponding to half the minimum and maximum intended compressed diameters as recommended by the manufacturer in the product literature between the testing plate and the center of the optic

NOTE - The frequency may be adjusted depending on how well sinusoidal behavior of the material is achieved (i.e., if it is verified that the loop follows the testing plate without lag at all times).

A suggested method for dynamic fatigue durability testing is described in ISO 11979-3 Annex G with the additional proviso that the surface and bulk homogeneity characteristics regarding the appearance of fractures and/or stress lines in the loops at the points of stress concentration in the test be described.

#### **5. Out-of-optic plane bending strength**

For RIs utilizing iris fixation, a specification for the minimum force for the out-of-optic plane bending/flexing strength of all supports should be established. This specification is intended to provide additional characterization of the implant design.

#### **6. Folding/injection testing**

RIs that are folded and/or delivered from an injector system for implantation should be evaluated with all the folding instruments/injector systems that a sponsor includes as recommended for the device. There should be no change in the optical and physical properties of the device as a result of the folding/delivery. Minimum testing recommendations are outlined below.

- a. Dioptric power and imaging quality
- b. Overall diameter and sagitta if the loops are engaged/stressed during folding and/or delivery
- c. Visual inspection of optics and loop(s)
- d. Evaluation of the fold recovery time
- e. Evaluation of acceptable amount of time for which the device may remain folded; testing should be done for a minimum of three minutes. This information should be included in the labeling. If testing is performed for twenty minutes or longer, no time limit is needed for the labeling.

Testing should be performed on at least ten devices each of both the highest and lowest powers (or dimensions) with recommended lubricating solutions (i.e., viscoelastics or saline). The characteristics of the device post-folding/delivery should be within the final product specifications.

**7. Surface and bulk homogeneity**

The RI should be essentially free from surface and bulk defects and all edges should appear smooth when viewed at 50x magnification with a stereo microscope using optimal lighting conditions.

**8. Additional material properties**

For purposes of characterizing material properties for shelf life studies and other validations, specifications for the bulk mechanical properties (e.g., tensile strength, elongation at break) should be established.

**V. Sterility Testing**

**A. General**

All testing should be performed on the finished product as marketed. The test methods specified below are suggested methods. Alternative sterilization and test methods are permitted if appropriately validated. The omission of certain tests should be justified with a valid scientific argument/rationale.

**B. Validation of Sterilization Method**

1. Steam Sterilization -

Validation of steam sterilization should be carried out in accordance with the requirements of ISO 11134.

2. Ethylene Oxide (EO) Sterilization -

Validation of EO sterilization should be carried out in accordance with the requirements of ISO 11135.

Sponsors may perform parametric release of EO-sterilized lenses by providing a validation that includes:

- the parametric release requirements specified in ISO 11135;
- documentation of the successful completion of end product sterility testing, pyrogen testing and EO residual testing on all lots produced over one calendar year
- documentation that each sterilization cycle that was run during the same calendar year met cycle specifications

Note - For sponsors with sterilization and storage in stable climates (with little or no seasonal temperature or humidity variations), six months of the documentation described above is sufficient

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### 3. Radiation Sterilization -

Validation of radiation sterilization should be carried out in accordance with the requirements of ISO 11137.

### 4. RI Bacteriostasis/Fungistasis testing -

Bacteriostasis/fungistasis testing should be carried out in accordance with the requirements of USP 24, <71>, 2000).

### 5. Bacterial Endotoxins -

Bacterial endotoxin testing should be conducted in accordance with a validated bacterial endotoxin test that includes an inhibition/enhancement test (see: USP 24, <85>, 2000).

Acceptable bacterial endotoxin concentration levels are described in FDA Guideline: "[Validation of Limulus Amebocyte Lysate Test as an End-Product Endotoxin Test for . . . Medical Devices](#)," December 1987.

### 6. Package Integrity Testing -

Package integrity testing should be performed regardless of sterilization method and may consist of either of the following:

- a microbial barrier test in combination with a validated seal integrity test; or
- a validated whole package physical integrity test in combination with a validated seal integrity test.

Examples of package integrity testing can be found in ISO 11607, ASTM F1585-95, ASTM F1929-98, ISO 2248, and ISO 8318. References for microbial barrier testing can be found in the following articles, published in Medical Device & Diagnostic Industry (MDDI):

1. Placencia, Ana M. et al, "FDA Exposure Chamber Method," May, 1986.
2. Reich, Robert R., "A Method for Evaluating the Microbial Barrier Properties of Intact Packages," March, 1985.
3. Schneider, Philip M., "Microbial Evaluation of Package and Packaging Material Integrity," May, 1980.

## **C. Product Release Testing**

The following testing should be performed on each manufacturing lot.

### 1. Sterility -

Sterility testing should be conducted in accordance with a validated sterility test that includes a Growth Promotion Test (see USP 24, <71>, 2000).

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### 2. Bacterial Endotoxins -

Bacterial endotoxin testing should be conducted in accordance with a validated bacterial endotoxin test (see: USP 24, <85>, 2000).

Acceptable bacterial endotoxin concentration levels are described in FDA Guideline: "[Validation of Limulus Amebocyte Lysate Test as an End-Product Endotoxin Test for . . . Medical Devices](#)," December 1987.

### 3. Ethylene Oxide Residual Testing

EO residual testing should be carried out in accordance with ISO 10993-7 (1995) and the draft AAMI TIR (Technical Information Report) for ISO 10993-7. As described in paragraph 4a., for refractive implants that are not the same size as IOLs, the limit for residual ethylene oxide should be pro-rated on the basis of the mass of the device, with the mass of an IOL taken as 20 mg. The following modifications should also be implemented:

- The procedure should consist of a solvent exhaustive extraction or a head space exhaustive extraction.

Note - Sponsors should choose a solvent that adequately swells or dissolves the lens material to facilitate extraction of the ethylene oxide molecules. A headspace method may be used if it has been validated to demonstrate that the extraction is as exhaustive as a solvent method. Alternatively, a sponsor may demonstrate the relative efficiency of an extraction method and adjust the internal release specifications accordingly.

- The ethylene chlorohydrin (ECH) residue in refractive implants that resemble IOLs should not exceed 2.0 µg ECH per lens per day, not to exceed 5.0 µg per lens. For those RIs that are not the same size as IOLs, the limit for residual ECH should be pro-rated on the basis of the mass of the device, with the mass of an IOL taken as 20 mg.

Note 1 - Ethylene glycol residues should be sufficiently controlled by the limits set for ethylene oxide and ethylene chlorohydrin residues.

Note 2 - Initially, EO residual testing should be performed on every lot. However, sponsors may provide historical data to support a request for less frequent testing (e.g., quarterly, semiannually).

## **VI. Shelf Life and Shipping Testing**

### **A. General**

The test methods specified below are suggested methods. Alternative methods are permitted if appropriately validated. The omission of any tests should be justified with a valid scientific rationale.

A study protocol should be developed prior to initiation of the study.

The study should demonstrate that the parameters assessed with regard to safety and efficacy are within the original manufacturing specifications at the conclusion of the study. If a manufacturer wishes to maintain the possibility to resterilize finished RI lots, the finished RI lot(s) used in the stability study should have undergone the maximum number of sterilization cycles allowed under the manufacturer's procedures.

## **B. Materials and Methods**

### 1. Test Samples -

The manufacturing lot(s) used for the stability study should be representative of normally produced manufacturing lots, and be packaged in the manner intended for marketing. A minimum of 10 lenses per test should be evaluated. Seal/closure integrity and microbial barrier testing may be performed on packages without an included RI. However, microbial barrier testing should also include 10 negative controls and 1 positive control.

The number of RI lots and the diopter range of the test samples should be in accordance with the provisions in Annex D.

Note 1 - In certain cases, more than one of the tests listed in Annex D may be performed on a single RI (e.g., if required, dioptric power, imaging quality and spectral transmission may all be measured on the same RI), thereby reducing the total number of devices needed.

Note 2 - When the manufacturing method does not allow different finished device lens lots to be produced within a reasonable time, a subdivision of one finished device lot into sub-lots may be employed in the studies. (Refer to the definition of "finished device lots.")

### 2. Analytical Methods -

Suitable analytical methods should be chosen for the tests indicated in Annex D and for any additional tests contained in the study protocol. The methods selected should be recorded. If a method is selected that is not included among those listed in Annex B of ISO/DIS2 11979-6 or those recommended in other parts of this guidance document, the method and the details of its validation, demonstrating the capability of the method, should also be documented.

## **C. Real-time Shelf-life Studies**

For one of the finished device lots, the tests chosen from Annex D should be carried out initially and at intervals in accordance with the protocol up to and including the manufacturer's desired expiration date. The other finished device lots should be tested at least initially and at the desired expiration date.

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The parameters measured should remain within the specified limits of the applicable parts of this guidance document. In case there are no limits specified in this guidance document, the parameters measured should remain within the manufacturer's internal finished product release specifications. If, during the course of the study, a parameter is found no longer to conform to the specifications at two or more time intervals, the maximum shelf-life of the refractive implant under study has been reached at the last conforming measurement point.

### 1. Product Stability Studies -

Annex D lists tests that should be performed depending on RI type. If a specific test listed in Annex D has not been carried out, the justification for the omission should be provided.

Testing for changes due to interaction with the packaging material should be considered, as should testing for changes in the concentration of additives and coatings in addition to those listed in Annex D.

### 2. Package Integrity Studies -

As listed in Annex D, package integrity testing should consist of a validated seal integrity test in combination with microbial barrier test or a validated whole package physical integrity test. Examples of methods for physical integrity testing, some of which may have been previously validated, can be found in ISO 11607.

## **D. Accelerated Shelf-life Studies**

Studies performed under accelerated conditions are likely to speed up any degradation processes, and therefore permit extrapolation of intervals under accelerated conditions to intervals at normal storage conditions. For microbial barrier testing, the accelerated conditions should involve storage at a specified temperature and with a relative humidity of at least 40%. If a sponsor wishes to perform sterility testing in lieu of microbial barrier testing, the storage temperature should be no higher than 45°C. The corresponding real-time shelf-life is calculated by multiplying the studied time period by  $1.8^{(T_a - T_o)/10}$ , where  $T_a$  is the accelerated temperature and  $T_o$  is the typical storage temperature (usually room temperature).

Accelerated studies should be carried out in the same way as real-time studies with the exception of the conditions chosen. It is important that lenses to be measured be allowed to equilibrate to the same conditions as at the initial measurements before being tested.

Note - RIs which have been aged under real-time conditions may be aged further under accelerated conditions. The established shelf-life would be the length of the real-time testing plus the real-time equivalent of the accelerated testing.

FDA prefers that real-time testing be performed for establishing shelf life; however, we have historically accepted up to 5 years of accelerated testing without corresponding real-time testing for PMMA and cross-linked polydimethylsiloxane implants, such as IOLs, that are packaged in Tyvek pouches. A scientific rationale should be provided to establish a shelf-life beyond 5 years through accelerated testing without corresponding real-time data.

For new materials, real-time testing should be performed.

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Note - Sponsors may submit a rationale to support accelerated testing (without corresponding real-time testing) for RIs made of materials other than PMMA or cross-linked polydimethylsiloxane. The rationale should demonstrate that the material has a history of use in ocular implants, such as IOLs, that have been produced by more than one manufacturer.

### **E. Shipping Tests**

In view of the temperature fluctuations that can occur during shipment, the manufacturer should consider the maximum and minimum temperatures that the RI is designed to withstand. The manufacturer should obtain data and records to demonstrate that the RI remains within its specifications having been exposed to the maximum temperature for 24 hours and similarly, after having been exposed to the minimum temperature for 24 hours. Alternatively, the manufacturer should study the implants at the temperatures and durations described in ASTM D-4169-94.

The tests that should be performed in the shipping studies are listed in Annex D. The drop and vibration testing listed in Annex D should be performed according to the methods described in ISO 2248 and ISO 8318. Both the package and the product should be inspected following these tests and the packaged product should be considered to have satisfactorily passed the test if, upon examination, the product is free from damage and the container still affords functional protection to the content.

## **VII. Clinical Investigation**

### **A. General**

The requirements described in 21 CFR Part 812 apply to the clinical investigations of refractive implants.

### **B. Elements of the Clinical Protocol**

The following are elements of a clinical protocol that may be used to collect sufficient, relevant and appropriate data to determine the safety and effectiveness of refractive implants.

#### **1. Study Objectives**

The sponsor should outline the objectives of the clinical investigation. These objectives should include the collection of safety and effectiveness data to support a premarket approval application (PMA). The proposed indications for use of the RI should be stated.

Note: Sponsors that intend to include mixed astigmatism as an indication should be aware that FDA may recommend additional safety and/or efficacy endpoints.

#### **2. Risk/Benefit Analysis**

The risk/benefit analysis should provide a description and analysis of all risks to which

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the subjects will be exposed, how those risks will be minimized and a justification for the investigation. Additionally, the expected risks and benefits of the new device should be compared to other available options for refractive correction (such as RK, PRK, LASIK, spectacles, contact lenses).

### 3. Study Endpoints

#### a. Safety Endpoints and Target Values

The following safety endpoints and target values are only recommendations; certain refractive devices may pose different safety concerns and therefore, additional or fewer safety endpoints may be appropriate.

##### Maintenance of Endothelial Cell Counts

- Endothelial cell loss as measured between the preoperative and the Month 3 postoperative visit should not exceed 10%.
- Endothelial cell loss between the Month 3 and Month 36 exam should be reported and should not exceed 4.125% (equivalent to 1.5% per year).

##### Maintenance of Best Spectacle-Corrected Visual Acuity (BSCVA)

- <5% of eyes should lose 2 lines or more BSCVA (or BCLVA, where appropriate - see Section 7 below)
- <1% of eyes should have BSCVA (or BCLVA, where appropriate - see Section 7 below) worse than 20/40 (if 20/20 or better BSCVA preoperatively)

#### **Induced Manifest Refraction Cylinder**

- For those RIs that are not intended to correct pre-existing cylinder, <1% of eyes should have an induced manifest refractive astigmatism of greater than 2 D of absolute cylinder.

#### **Adverse events**

- The rates of adverse events associated with refractive implants, including cataract formation, should be reported.

#### b. Effectiveness Endpoints and Target Values

The following effectiveness endpoints are only recommendations. Sponsors wishing to make an additional marketing claim (beyond the indication(s) supported by the following endpoints) should include additional effectiveness endpoint(s) to substantiate the claim.

##### Predictability of Refraction

- 75% of eyes should achieve predictability (attempted versus achieved) of the MRSE of  $\pm 1.00$  D
- 50% of eyes should achieve predictability (attempted versus achieved) of the MRSE of  $\pm 0.50$  D.

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### Uncorrected Visual Acuity (UCVA)

- 85% of eyes should achieve an UCVA of 20/40 or better (for those eyes with BSCVA of 20/20 or better preoperatively).

#### 4. Study Design

The study design, including the sample size, duration of the study, proposed phased enrollment, and any plans for fellow eye implantation should be described. FDA recommends that separate protocols be submitted for each indication to be studied (e.g., myopia, hyperopia, presbyopia, myopia with myopic astigmatism, mixed astigmatism, etc.).

##### a. Sample Size

###### i. Safety and Effectiveness Study

The sample size for this study should be adequate to evaluate the rates of adverse events associated with refractive implants. Experience with aphakic IOLs and their associated adverse event rates demonstrates that a sample size of 300 subjects provides adequate precision for adverse events occurring at rates of 0.1% or greater (see FDA Draft IOL Guidance, October 14, 1999 and ISO/DIS 11979-7, Annex B). The maximum number of subjects enrolled in any study should be limited to no more than 143% of the sample size that the sponsor intends for the study.

After all of the subjects needed for a study have been enrolled, the sponsor may request approval to enroll additional subjects into a modified core study of the device so that investigators may continue their experience with the device until any premarket approval is obtained.

###### ii. Endothelial cell counts substudy

The loss of endothelial cells over time should be determined by evaluating measurements taken at the Month 3 (or Month 6) through Month 36 exams. A sample size of 200 subjects should be sufficient to detect a yearly endothelial cell loss of 1.5% and to demonstrate linearity of the cell loss over time (see Section 9 below).

###### iii. Contrast sensitivity/low contrast acuity substudy

For the analysis of contrast sensitivity loss, a sample size of approximately 125 subjects is recommended (see Section 9 below).

##### b. Number of investigators

Each investigator should contribute a minimum of 20 subjects to the study population, but not more than 25% of the subjects in the study.

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### c. Study Duration

A study duration of three years is recommended to adequately evaluate the maintenance of endothelial cell counts and the rate of cataractogenesis.

### d. Lost to follow-up

The lost to follow-up patients should comprise less than 10% of the study population after one year, and less than 30% of the study population after three years.

### e. Enrollment

The following phased enrollment plans are recommendations only. Depending on the design of the refractive implant, a different phase-in may be recommended. For example, if a significant design change is required for an additional indication, a slower phase-in may be necessary.

Note: Sponsors may wish to provide a scientific rationale to begin enrollment with Phase II. This rationale may consist of results from well-documented clinical trials conducted outside of the U.S.

For clinical studies for a single refractive indication:

- Phase I - 10 subjects, followed for 6 months
- Phase II - 100 additional subjects, with a report to FDA when 50 subjects have been followed for 6 months and all 110 subjects have been enrolled
- Phase III - remainder of study population

For clinical studies of more than one refractive indication (e.g., myopia and hyperopia or myopia and myopia with myopic astigmatism) ongoing simultaneously:

- Phase I - 20 subjects (no more than 10 of each indication), followed for 6 months
- Phase II - 150 additional subjects (no more than 100 per indication). A request to expand the enrollment for one indication may be submitted when 50 subjects with that indication have been followed for 6 months. The report should include data for all subjects enrolled for the particular indication.
- Phase III - The remainder of the study population for an individual indication.

For clinical studies of RIs that provide astigmatic correction (in addition to a spherical correction), where substantial clinical data has been collected for the spherical correction:

- Phase II – 100 subjects, with a report to FDA when 50 subjects have been followed for 6 months and all 100 subjects have been enrolled.

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- Phase III – remainder of the study population needed to demonstrate effectiveness of the cylindrical correction

### f. Bilateral Implantation

FDA has concerns about exposing both eyes to a new device without some prior clinical safety information. Therefore, bilateral implantation should not be performed during Phase I. Sponsors should attempt to enroll contact lens tolerant subjects in the Phase I to avoid difficulties with anisometropia. The informed consent document should state clearly that bilateral implantation will not be available early in the investigation. A prospective protocol waiver may be submitted for bilateral implantation of a Phase I subject, but should contain a strong clinical rationale.

At the time that expansion to Phase III is approved, sponsors may wish to allow implantation of the fellow eye, under the following conditions:

- no adverse events in the initially implanted eye
- with a waiting period of 90 days between eyes
- with signed informed consent document specifically for fellow eye implantation

Sponsors may wish to provide additional information as a rationale for a shorter waiting period between eyes. Additionally, prospective protocol waivers may be submitted for those subjects for whom the investigator believes fellow eye implantation with less than 90 days between eyes is necessary.

### g. Implant Exchanges

During the investigation, the implant may be removed (without replacement) at any time at the request of the subject or if the investigator believes it appropriate. However, FDA believes that implant exchanges should be limited in number so as to preserve the integrity of the clinical data and to prevent an undue lengthening of the study.

At the time that expansion to Phase III is approved, sponsors may wish to allow exchanges when certain criteria have been met. The criteria for exchanges should include a waiting period based on the point of refractive stability and any other longer-term safety concerns. Prior to Phase III, prospective protocol waivers may be submitted for those subjects for whom the investigator believes an implant exchange is necessary.

## 5. Study Population

The following are recommended inclusion criteria for studies of refractive implants:

- myopic subject is >18 years of age, < 45 (ideally) or 50 years of age (to avoid age-related cataract formation as a confounding variable)

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- hyperopic subject is >18 years of age, <60 years of age (given the older average age of hyperopes and difficulties in enrollment)

Note: Sponsors wishing to enroll hyperopic patients older than 50 should modify the informed consent document to note the increased likelihood of cataract formation with advancing age.

- subject meets specified refractive criteria (spherical and cylindrical components)
- subject has specified minimum BSCVA in each eye and UCVA 20/40 or worse
- hyperopic subject has less than 0.75 D difference between cycloplegic and manifest refraction
- subject has had a stable correction ( $\pm 0.5$  D), as determined by MRSE for a minimum of 12 months prior to surgery, verified by consecutive refractions and/or medical records or prescription history.
- subject, whose current method of correction is contact lenses, has demonstrated a stable refraction ( $\pm 0.5$  D), as determined by MRSE, on two consecutive exam dates. Stability of the refraction is determined by the following criteria: a) lenses were not worn for at least 2 weeks (rigid and toric contact lenses) or 3 days (soft contact lenses) prior to the first refraction; b) the two refractions were performed at least 7 days apart. (Contact lens wearers should also have demonstrated preoperative stability as defined above.)
- subject, age 21-45, has at least 2500 endothelial cells as determined by specular microscopy; subject, age 46 or older, has at least 2000 endothelial cells as determined by specular microscopy
- subject, with a significant cylindrical refractive error, who would receive an RI providing spherical correction only, has been given the opportunity to experience his/her best spectacle vision with spherical correction only and is willing to proceed with the surgery
- subject has given written informed consent
- subject is willing and able to comply with schedule for follow-up visits

The following are recommended exclusion criteria for studies of refractive implants:

- subject has an acute or chronic disease or illness that would increase the operative risk or confound the outcome(s) of the study (e.g., immunocompromised, connective tissue disease, clinically significant atopic disease, diabetes, etc.)
- subject is taking systemic medications that may confound the outcome of the study or increase the risk to the subject, including, but not limited to steroids, antimetabolites, etc.
- subject has history of corneal disease (e.g., herpes simplex, herpes zoster keratitis, etc.)
- subject has had previous intraocular or corneal surgery that might confound the outcome of the study or increase the risk to the subject
- subject has evidence of retinal vascular disease and/or a history of hypercoagulability
- subject has an ocular condition (such as prekeratoconus or keratoconus, recurrent erosion syndrome or corneal dystrophy) that may predispose the subject to future complications

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- subject has glaucoma or is suspected of having glaucoma by exam findings and/or family history
- subject of childbearing potential is pregnant, plans to become pregnant, or is lactating during the course of the study, or has another condition associated with the fluctuation of hormones that could lead to refractive changes

6. Surgical Procedure

The clinical protocol should include a description of the surgical procedure, including the power formula to be used and a scientific explanation of its derivation. FDA strongly encourages sponsors to allow personalization of the power formula and to collect this information on the case report forms. The clinical data should be evaluated at intervals during the study to validate the accuracy and to refine the power formula if necessary.

Intraoperative use of viscoelastics and the preoperative, intraoperative and postoperative medications should be standardized in the protocol. Wound placement/size, the use of sutures, and whether an iridectomy/iridotomy is to be performed should also be standardized. If any of these variables are left to the surgeon's discretion, the case report forms should record this information and the final data analysis should include stratification by operative variable(s).

7. Reporting Periods and Evaluations

- a. The following reporting periods are suggested:

Preoperative	Month 3 (10-14 weeks)
Operative	Month 6 (21-26 weeks)
Day 1 (1 day)	Month 12 (11-14 months)
Week 1 (5-9 days)	Month 24 (23-27 months)
Month 1 (3-5 weeks)	Month 36 (35-39 months)

- b. The following evaluations should be performed (see Annex E for recommended examination schedule):

For all subjects:

- UCVA (distance and near)
- BSCVA (distance and near)

Note: Sponsors may wish to perform best contact lens corrected visual acuity (BCLVA) on high myopes and hyperopes to increase the accuracy of preoperative refractions and power calculations.

- Manifest and cycloplegic refractions
- Subject questionnaire - should include questions regarding visual symptoms, spectacle/contact lens wear, and functional visual performance (night driving, reading, etc.)
- Intraocular pressure
- Slit lamp exam
- Gonioscopic exam

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- Dilated fundus exam – should include exam for the presence of retinal tears
- Mesopic pupil size
- Pachymetry
- Topography (if the cornea may be altered due to the device or the surgical procedure)
- Axial length measurement (preoperatively)
- Anterior chamber depth (ACD) measurement (if inclusion/exclusion criteria include a minimum or maximum ACD)
- Keratometry (to establish preoperative refractive stability for CL wearers and to demonstrate postoperative corneal stability where necessary)
- Assessment of natural lens for cataractogenesis

On a subset of subjects:

- Specular microscopy
- Contrast sensitivity or low contrast acuity testing - mesopic and mesopic with glare conditions

### c. Testing Methodologies

#### i. Visual Acuity

Visual acuity testing should be performed using a logarithmic chart, e.g., ETDRS or equivalent. The same type of chart and testing distance should be used for all testing centers. The chart background luminance should be approximately 85cd/m<sup>2</sup> (80-160 cd/m<sup>2</sup> is acceptable), and should be identical for all testing centers within an IDE study. Ambient illumination should be from dim to dark. No surface (including reflective surfaces) within the subject's field of view should exceed the chart background in luminance.

Refractions should be expressed using the following conventions. Hyperopia with hyperopic astigmatism should be expressed as + sphere + cylinder. Myopia with myopic astigmatism should be expressed as – sphere – cylinder.

#### ii. Specular Microscopy

Maintenance of endothelial cell counts is considered to be the primary safety endpoint for studies of refractive implants. FDA's main concern is the possibility of a chronic loss of endothelial cells, that, even at a low yearly rate could, over time, lead to corneal edema and decompensation. FDA has estimated that with an initial loss due to surgical trauma of 10% or less, a subsequent yearly loss of 1.5% or less should preserve the integrity of the cornea over the life of the subject.

To determine endothelial cell loss, specular microscopy should be performed preoperatively and at the Month 3 (or Month 6), Month 12, Month 24, and Month 36 exams. Losses due to surgical trauma may be

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determined by evaluating the cell counts at Month 3 (or Month 6) in comparison to the preoperative measurements. To determine losses over time, measurements from the Month 3 (or Month 6) and later time points should be analyzed.

A yearly rate of cell loss may be determined by subtracting the measurement at Month 3 from the measurement at Month 36 and dividing by 2.75 years (using Month 6 data, divide by 2.5 years). However, to apply this rate of loss to the remainder of the life of the device requires an assumption that the loss of cells after Month 3 (or Month 6) occurs in a linear fashion. Therefore, the sample size chosen for this study should be sufficient to detect a yearly loss of 1.5% as well as to demonstrate the linearity of the cell loss over time (see Section 9 below).

### Collection of data

Prior to the beginning of the study, each investigational site should provide a set of consecutive images to the study monitor or sponsor to determine the current state of image quality and to rectify any problems. Cameras that output 35 mm slides, half-inch video, digitized images on disk or images sent by e-mail are acceptable. Cameras that can record digitized images on disk or to e-mail are preferable (for ease of data transfer).

Each site not using an internally calibrated camera (in which each image displays the calibration) should receive a calibration slide that defines both the X and Y axis; instructions on how to obtain the calibration image should be included. Calibration should be checked by the study monitor on at least a yearly basis. Additionally, the study monitor should perform periodic validation of the study site's methodology unless an automated camera is used. Calibration of the specular microscopes at the sites across the study should be performed by comparing cell density data from a standard set of images evaluated by each site. Different cameras may be used, but greater uniformity is expected with a single camera type.

A reading center is advisable, although not required. However, if a reading center is not used, the person responsible for taking and accepting the images should be certified for his/her ability to take high-quality images, and be adequately trained in both endothelial cell photography and in the evaluation of the images. If possible, the same trained and certified technician/photographer should be used at each site throughout the study. A backup technician who is trained and certified should also be available. At least 50 countable endothelial cells should be present in each image; two images from each subject are strongly recommended. The technician/photographer should use a standardized counting method for the determination of cell density. Fixed-frame analysis, variable frame analysis, a center method, a corner method, or auto-count may be used.

iii. Contrast Sensitivity

Contrast sensitivity or low contrast acuity testing should be performed under mesopic and mesopic with glare conditions. Contrast sensitivity should be measured at spatial frequencies as close as possible to 1.5, 3, 6, 12, and 18 cycles/degree. Low contrast acuity should be measured with charts with contrast levels as close as possible to 5%, 10%, and 50%. Subjects should be tested with BCLVA preoperatively, to prevent spectacle distortion and magnification/minification effects from biasing the results.

The chart luminance should be 3 cd/m<sup>2</sup> or less and the ambient illumination should be lower than the chart luminance. In order to limit pupil constriction and maintain uniform glare conditions across the test chart, the glare source should be an array of two or more small spots symmetrically positioned around the chart. The level of glare should be the minimum necessary to significantly reduce the contrast sensitivity of young adult subjects with normal corneas and normal vision, but the illumination should not be so great as to completely wash out the target in these young, normal subjects. The reduction in contrast sensitivity due to glare in normal subjects should be a mean loss of between 0.15 and 0.45 log units at 6 cycles/degree (for grating charts) or an approximate two line loss on a letter acuity chart of approximately 10% contrast. A small pilot study of normal subjects may be necessary to determine an appropriate glare level.

Control data may be obtained from preoperative measurements of best spectacle-corrected noncataractous eyes or from a sample of normal subjects with the same age, gender and refractive error distributions as the postoperative test subjects. The subject population should be large enough to detect a 0.3 log unit difference in contrast sensitivity. (See Section 9 for sample size calculations.)

iv. Evaluation of the Natural Lens for Cataractogenesis

The natural lens should be evaluated preoperatively and at each of the postoperative intervals for lens changes, including, but not limited to, the development of clinically significant lens opacities. A standardized grading system (e.g., Oxford or LOCS III - references below) and photographs are recommended to document lens changes.

Sparrow et al. The Oxford modular cataract image analysis system. *Eye* 1990; 4:638-48.

Chylack et al. The lens opacities classification system III. The longitudinal study of cataract study group. *Arch Ophthalmol* 1993; 111:831-6.

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v. Mesopic Pupil Size

Pupil size should be measured for all eyes in the study, with eye illumination identical to that used for mesopic contrast sensitivity testing. The measurements should be made with an infrared pupillometer or other calibrated infrared camera. Contrast sensitivity and pupil measurement should begin only after the eye has had time to fully adapt to the testing conditions (approximately 10 minutes).

vi. Slit Lamp Exam

The slit lamp exam should include the measurement of aqueous cell and flare by a standard grading system, a gonioscopic exam, and evaluation for the presence of corneal edema, pupillary irregularities, iris atrophy and pigment dispersion.

The following system is recommended for grading of aqueous cell and flare using a slit beam 0.3 mm wide and 1.0 mm long:

Cells

none	(0)	= no cells seen
mild	(+1)	= 1-5 cells seen
moderate	(+2)	= 6-15 cells seen
severe	(+3)	= 16-30 cells seen
very severe	(+4)	= > 30 cells seen

Flare

none	(0)	= No Tyndall effect
mild	(+1)	= Tyndall effect barely discernible
moderate	(+2)	= Tyndall beam in anterior chamber is moderately intense
severe	(+3)	= Tyndall beam in anterior chamber is severely intense
very severe	(+4)	= Tyndall beam is very severely intense. The aqueous has a white and milky appearance.

vii. Measurement of Intraocular Pressure

Intraocular pressure should be measured using Goldmann applanation tonometry. Other methods may be used with a scientific justification, but the same method should be used throughout the study. Additionally, the development of alternate methods may be necessary for refractive implants that alter the cornea such that commonly used methods may not be accurate.

viii. Patient Questionnaire

A patient questionnaire should be administered to all patients. The questionnaire should include questions regarding glare, halos, double

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vision, spectacle/contact lens use and night driving. The time of onset of visual symptoms should also be addressed.

At the time this document is being written, there are no validated patient questionnaires specifically addressing refractive surgery issues that have been published. Until references to published validated questionnaires are available, FDA recommends that a validated questionnaire that addresses visual function following ophthalmic surgery be used, with questions specifically relating to refractive surgery issues be written in the same format and added to the questionnaire.

8. Adverse Events

Reports of unanticipated adverse device effects shall be reported to the sponsor and the reviewing IRB within 10 days of the investigator's learning of them, and to FDA and all reviewing IRBs and participating investigators within another 10 days of the sponsor's learning of them (see 21 CFR 812.150(a)(1) and 812.150(b)(1)). All other adverse events shall be documented in the case reports.

The following adverse events, although not an all-inclusive list, should be considered to be reportable as described in 21 CFR 812.150(b)(1).

Endophthalmitis  
Pupillary block  
Retinal detachment  
Corneal ulceration/infectious infiltrate  
Stromal thinning/corneal melting  
Corneal haze/cloudiness, if associated with  $\geq 2$  lines BSCVA loss  
Secondary surgical intervention\*  
Extrusion of the device

\* Note: Secondary surgical interventions should be reviewed by the sponsor on a case-by-case basis to determine if reporting is appropriate.

Additionally, the sponsor should provide a list of possible adverse events, including any that apply from the list below, that may occur in conjunction with the investigational device. The clinical report forms should include forced-choice listings of these adverse events and allow for the recording of other adverse events not listed.

Hyphema	Epithelial defect
Macular edema	Epithelial inclusion cyst
Corneal scarring	Epithelial ingrowth
Uveitis/Iritis	Corneal haze/cloudiness
Conjunctivitis	Corneal infiltrates - sterile
Raised IOP requiring treatment	Corneal edema
Vitreous loss (intraoperative)	Dislocation of device
Central corneal sensation loss	Induction of cataract
Corneal neovascularization - pannus or deep vessel	

9. Data Analysis/Statistical Methods

a. Sample Size Determination

i. Maintenance of endothelial cell counts

The loss of endothelial cells over time should be determined by evaluating measurements taken at the Month 3 (or Month 6) through Month 36 exams. Two measurements should be taken at each visit and the mean cell count should be used. The number of subjects should be sufficient to detect a yearly endothelial cell loss of 1.5% and to demonstrate linearity of the cell loss over time.

One approach to determining an appropriate sample size is to set an upper bound of the 90% confidence interval (C.I.) around the observed loss using the following formula:

$$\text{Upper 90\% C.I.} = X + Z\alpha(\sigma/\sqrt{N})$$

where  $X$  is the observed total cell loss after 2.75 years (then divided by 2.75 to calculate the yearly loss),  $Z\alpha = 1.28$  for a one-sided upper 90% C.I.,  $\sigma$  is the assumed standard deviation of 5%, and  $N$  is the sample size.

If the upper bound is set to 4.125% (representing a 1.5% per year loss) and a standard deviation of 5% is assumed, a sample size of 200 subjects would ensure with 90% confidence that the true population loss is 1.5% per year or less. The observed loss must be greater than 1.33% per year for the 90% C.I. to exceed 4.125%. A sample size of 200 subjects should also be sufficient to demonstrate linearity.

ii. Contrast Sensitivity Testing

Contrast sensitivity losses should be determined by comparing measurements obtained at the Month 3 or Month 6 visit (depending upon when refractive stability is demonstrated) and at the Month 36 visit with preoperative measurements. The sample size should be sufficient to detect a 0.3 log unit loss, assuming a 0.2 log unit standard deviation. Tolerance limits may be used to establish with a certain level of confidence (e.g., 90%) that a reasonable percent (e.g., 95%) of the population has losses below the largest observed value in the sample (hopefully, 0.3 log units).

If the tolerance limit is set to  $\leq 0.3$  log units, then assuming  $\bar{x} = 0$  (under the null hypothesis of no loss) and  $s = 0.2$ , solving for  $K$  in the following equation:

$$\bar{x} + Ks \leq 0.3$$

$$0 + K(0.2) \leq 0.3$$

$$K = 1.5$$

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Using this value for *K*, with appropriate statistical tables, an estimated sample size of approximately 80 would afford about 90% confidence that 95% of the losses would be below 0.3 log units. Since the value of 80 is an estimate, FDA recommends enrolling 125 subjects in this substudy.

b. Accountability

For further information, sponsors are referred to FDA’s draft guidance document, “Accountability Analysis for Clinical Studies for Ophthalmic Devices” (Federal Register notice dated August 4, 1999, <http://www.fda.gov/cdrh/ode/1350.pdf>).

A PMA should not be submitted until at least 80% of subjects enrolled have become eligible for the final visit (i.e., 20% or fewer subjects remain active).

Tables showing the overall accountability (at the last visit) and accountability by postoperative visit should be presented. Suggested formats follow:

**Overall Accountability**

	Total	Percentage n/N
Enrolled (N)		
Available for Analysis		
Day 1		
Week 1		
.		
.		
.		
Missing subjects at (final visit)		
Discontinued		
Missing (final visit) but seen at a later visit		
Not seen but status obtained (e.g., by phone)		
Lost to follow-up		
Active		

**Accountability by Postoperative Visit**

		Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
Available for Analysis	n/N (%)					
Discontinued	n/N (%)					
Active	n/N (%)					
Lost to follow-up	n/N (%)					

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% Accountability =  $\frac{\text{Available for Analysis (Enrolled-Discontinued-Active)}}{N = \text{total eyes enrolled}}$					
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c. Data Presentation/Analyses

The following analyses, although not an inclusive list, are recommended for submission in the PMA.

i. Stability of Manifest Spherical Equivalent Refraction (MRSE)

The sponsor should calculate the number of subjects who have:

- a change of less than or equal to 1.00 D of MRSE between two refractions performed at least 3 months apart
- a change of less than or equal to 0.50 D of MRSE between two refractions performed at least 3 months apart

The sponsor should calculate the mean change in MRSE between visits as determined by a paired analysis. This value should ideally be 0.025 D per month or less.

ii. Maintenance of Endothelial Cell Counts

The sponsor should perform the following analyses:

- mean rate of cell loss over time, calculated via a paired analysis in order to calculate the mean of the differences
- frequency analysis examining the percentage of patients who lose greater than 10% of cells between Month 3 (or Month 6) and Month 36

iii. Evaluation of the Natural Lens for Cataractogenesis

Analyses should include:

- the percentage of subjects with lens changes (i.e., any change in the appearance of the lens, with stratification by the type of change)
- the percentage of subjects with clinically significant lens opacities (defined as opacities leading to a loss of 2 or more lines of BSVCA with glare as compared to preoperative levels adjusted for magnification/minification effects)

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### iv. Maintenance of Contrast Sensitivity

The sponsor should perform the following analyses:

- at each spatial frequency (or at each contrast level for low contrast acuity testing), the mean change in contrast sensitivity/acuity between preoperative and postoperative measurements as determined by paired analyses
- the number of subjects who have a loss  $>0.3$  log units at two or more spatial frequencies
- at each spatial frequency or contrast level, the results with glare versus without glare
- results stratified by mesopic pupil size

### v. Additional Analyses

The following additional analyses are recommended:

- Preoperative demographics - gender, race, eye treated (left or right), age, contact lens history
- Dataline subject listings of protocol deviations
- Last reported status (UCVA, BSCVA, MRSE) of discontinued subjects (excluding subjects who were retreated)
- Last reported status (UCVA, BSCVA, MRSE) of lost to follow-up subjects
- Summary of the safety and effectiveness variables listed in B.3 above by exam (including 95% C.I. for each value)
- Change in BSCVA at each exam, stratified by lines of loss or gain (+1, +2 >+2, -1, -2, >-2) with dataline listings for those subjects who lost 2 or more lines
- UCVA at each visit - stratify by intended postoperative refraction (emmetropia vs. intentional undercorrection)
- Change in IOP from preoperative levels (increase 1-5, 6-10,  $>10$  mmHg, and decrease 1-5, 6-10,  $>10$  mmHg)
- For cylindrical corrections:
  - accuracy of spherical component and accuracy of cylindrical component
  - stability of MR cylinder
  - subjects with residual astigmatic error

### **VIII. Labeling**

A “label” is defined as a display of written, printed or graphic matter upon the immediate container of any article. For medical devices, the packaging and the package insert are the major components of the labeling. FDA recommends that sponsors provide physician and patient labeling for refractive implants.

The sale, distribution and use of refractive implants are restricted; therefore, the label must include the caution restricting the device to sale by or on the order of a physician. In accordance with the provisions of section 502(r) of the Federal Food, Drug, and Cosmetic Act (the act), advertisements and other descriptive printed material issued by the manufacturer, packer, or distributor with respect to a restricted device must include, but is not limited to, the following:

1. a true statement of the device’s established name (common or usual name unless there is an official name designated by FDA or recognized in an official compendium, printed prominently and in type at least half as large as that for any trade or brand name for the device; and
2. a brief statement of the intended uses of the device and relevant warnings, precautions, side effects, and contraindications.

References: Office of Device Evaluation (ODE), [Device Labeling Guidance](#), General Program Memorandum #G91-1

Code of Federal Regulations, 21, Chapter 1, Subchapter A, Part 1, Subpart B

ODE, Medical Device Labeling - Suggested Format and Content, Draft Guidance (available at <http://www.fda.gov/cdrh/ode/labeling.html>)

ODE, Medical Device Patient Labeling, Draft Guidance (available at <http://www.fda.gov/cdrh/humfac/1128.html>)

#### **Physician Labeling**

The following information should be included in labeling intended for the implanting physician.

#### **Device Description**

In this section, the labeling should include a brief description of the device, how it functions and its significant physical characteristics. The trade and generic names for the RI should be included.

#### **Indications**

The “indications for use” identify the target population of the device for which there is valid scientific evidence demonstrating the device’s safety and effectiveness.

#### **Contraindications**

Contraindications include situations in which the device should be not be used because the risk of use outweighs any possible benefit. Known (studied) hazards should be listed. For instance, a coating on a RI may be contraindicated for individuals known to be allergic to a component of the coating.

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### Warnings

FDA labeling guidelines state that the “Warnings” section should describe serious adverse events and potential safety hazards, limitations in use imposed by them, and steps that should be taken if they occur.

The labeling should include an appropriate warning if there is reasonable evidence of an association of a serious hazard with the use of the device. A causal relationship need not have been proved.

A warning is appropriate when the device is commonly used for a disease or condition for which there is a lack of valid scientific evidence of effectiveness for that disease or condition, and such usage is associated with a serious risk or hazard.

### Precautions

The “Precautions” section describes any special care that is to be exercised by the practitioner for the safe and effective use of the device. The sponsor should identify information to avoid certain risks in connection with implantation of the device, and information regarding the risks of reciprocal interference posed by the presence of the device during specific treatment. Precautions to be taken in the event of changes in the performance of the device that may be specific to the device should be described. Special patient populations that might be at risk or associated with a specific hazard should be identified in this section, as well as precautionary statements not appropriate for inclusion under other sections of the labeling.

### Adverse Events

An adverse event is defined as a predicted or unpredicted undesirable effect reasonably associated with the use of the device. For RIs, this section would include complications associated with the surgical implantation. This section should include all adverse events and directions to the other sections of the labeling for additional information regarding these adverse events. Adverse events experienced during the study of the device listed in descending order of frequency should be included in this section.

### Clinical Trial

The “Clinical Trial” section is used by an implanting physician to determine the risk/benefit ratio, reliability and performance standards of the RI. Information on the race and gender of the study population should be included.

This section should include a description of the clinical study design (number of subjects, date of initiation of the clinical trial, length of follow-up, etc.) and the results of each of the major safety and efficacy evaluations.

### Detailed Device Description

The package insert should contain a description of the RI, including material(s), power (if applicable), index of refraction (if applicable), UV transmittance (if applicable), dimensions, and any other distinguishing characteristics of the RI.

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The RI box (or outermost container) should also contain a detailed description of the RI. The following information should be included: manufacturer name and address, trade name of the RI, model number, lot/serial number, expiration date, power (if applicable), power constant (if applicable), dimensions, UV or non-UV (if applicable), and material(s).

FDA recommends that the inside container and/or pouch also include the manufacturer name, trade name of the lens, model number, lot/serial number, power (if applicable), and the statements “STERILE,” “Do not reuse,” and “Do not resterilize.”

### Directions for Use

This section should provide directions under which the practitioner can use the device safely and for the purpose for which the RI is intended. Details of any further treatment or handling needed before the device can be used should be included in this section. Information regarding the power constant or other means of power determination should also be included.

### **Patient Labeling**

The following information should be included in the patient labeling, written no higher than an 8<sup>th</sup> grade reading level, if possible. Sponsors are strongly encouraged to consult FDA’s Draft Guidance for Medical Device Patient Labeling.

### Device Description

The patient label should include a description of the device, where in the eye it is placed and a brief description of how it works. Graphics may aid in describing the device and/or its action.

### Indications for Use or the Purpose of the Device

The indications for use should be rewritten in lay terms and included in the patient label.

### Contraindications or When a Device Should Not Be Used

Situations in which the device should not be used should be clearly explained.

### Adverse Events/Risks of the Device

To make an informed choice about a medical device, a patient should have a thorough understanding of the effects and expectations of that device. The risks of the device, as determined in the clinical trial, should be clearly explained. Describe risks and benefits clearly and specifically and state both benefit and risk information in the same way (e.g., qualitative or quantitative), if possible. Balance risk and benefit information and present factual risk and benefit information without any attempt to influence the patient.

### Expectations of the Device and the Procedure Associated with the Device

Tell the patient what to expect before, during, and after a surgical procedure and/or the use of the device. If appropriate, give instructions on post-operative or post-procedural care.

### General Warnings and Precautions

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General warnings and precautions are the specific hazard alert information that a patient needs to know before receiving the device.

### Alternatives to the Device

When the patient has a choice among viable, effective, appropriate alternatives, the patient should be informed of the alternatives. If alternative devices or treatments are available that involve significant differences in such factors as risks, discomfort, or accuracy, information about the alternatives should be provided.

## **Annex A (normative) Genotoxicity test**

### **A.1 Purpose**

The purpose of this test is to determine the genotoxic potential of the test material.

### **A.2 General**

Testing of the genotoxic potential of materials to be used in refractive implants is essential unless materials already proven to be non-genotoxic are used, or if extracted compounds can be identified by suitable analytical methods and these compounds are known to possess no genotoxicity.

### **A.3 Test material**

The test material is described in A.3.1 of Annex A, ISO 11979-5.

### **A.4 Control material**

The control material is described in A.3.2 of Annex A, ISO 11979-5.

### **A.5 Equipment**

The equipment is described in A.3.3 of Annex A, ISO 11979-5.

### **A.6 Test procedure**

The test material is extracted with two different extractants, one of which is physiological saline, and the second a lipophilic or dipolar solvent.

The test material is extracted using the conditions specified in A.3.4 of Annex, ISO 11979-5.

The extracts are tested for genotoxicity in accordance with ISO 10993-3.

### **A.7 Test evaluation**

The test results are interpreted in accordance with ISO 10993-3.

## **Annex B (normative) Maximization sensitization test**

### **B.1 Purpose**

The purpose of this test is to assess the potential of the test material to produce sensitization.

### **B.2 General**

ISO 10993-10 gives general guidance on maximization sensitization testing. This annex defines the specific test conditions for testing refractive implants. ISO 10993-10 gives the necessary guidelines on how to carry out the actual testing.

### **B.3 Test material**

The test material is to be in the condition as intended for implantation, i.e., finished and sterile. If the manufacturer's instruction for surgical use specifies any form of treatment prior to implantation, the test material is treated accordingly. Otherwise no treatment, e.g., rinsing, is given.

### **B.4 Control material**

Suitable control samples.

### **B.5 Equipment**

The equipment is described in ISO 10993-10.

### **B.6 Test procedure**

The test material is extracted with two different extractants, one of which is physiological saline, and the second a lipophilic or dipolar solvent. Choose a lipophilic or dipolar solvent that does not dissolve or degrade the test material.

Prepare the extracts in accordance with Annex B of ISO 10993-10. Prepare suitable negative control samples in the same way. Subject the extracts to testing in accordance with ISO 10993-10.

Omit the preliminary tests described in clause 6.3.4.2 of ISO 10993-10 and carry out the procedure described in clause 6.3.4.3 of ISO 10993-10.

### **B.7 Test evaluation**

The test results are interpreted in accordance with ISO 10993-10.

## **Annex C (normative) Non-ocular implantation test**

### **C.1 General**

In accordance with ISO 10993-2, animal testing should be reduced to the justifiable minimum. Therefore, the appropriateness of applying animal tests should be assessed whenever new research work advances the state of scientific knowledge.

### **C.2 Purpose**

The purpose of this test is to demonstrate the tissue tolerance of the test material.

Note: ISO 10993-6 includes a series of well-established implantation tests, e.g., in subcutaneously or in muscle, which are suitable for refractive implants.

### **C.3 Test material**

Use either sterile finished refractive implants, or sterile facsimile material with a central thickness equivalent to that of a medium power refractive implant.

The test material is to be in the condition as intended for implantation, i.e., finished and sterile. If the manufacturer's instruction for surgical use specifies any form of treatment prior to implantation, the test material is treated accordingly. Otherwise no treatment, e.g., rinsing, is given.

### **C.4 Control material**

As negative reference material, high-density polyethylene or other suitable negative control plastic, recognized by pharmacopoeias, having about the same dimensions as the test material is used.

### **C.5 Test procedure**

The implantation procedure is carried out in accordance with ISO 10993-6.

#### **C.5.1 Test animals**

Justifications for the selection of the test procedure and the type of animal chosen (see ISO 10993-6) are recorded.

Note: One of the following species should be considered: mouse, rat, guinea pig or rabbit.

If the mouse is chosen, use only one implant per animal. With larger animals, use a maximum of eight implants per animal.

#### **C.5.2 Implantation period**

Assessment is done 4 weeks after implantation in accordance with ISO 10993-6.

Annex D (normative) Shelf-Life Test Table

RI Material	No. of finished device lots <sup>1</sup>	Dioptric power range <sup>2</sup>	Tests per study type (minimum 10 devices per lot)		
			Product stability	Package integrity <sup>3</sup>	Shipping stability <sup>4</sup>
All PMMA	1	Medium	<ul style="list-style-type: none"> <li>• Dimensions</li> <li>• Surface and bulk homogeneity</li> </ul>	<ul style="list-style-type: none"> <li>• Labeling</li> <li>• Seal integrity</li> <li>• Microbial barrier OR Whole package physical integrity</li> </ul>	<ul style="list-style-type: none"> <li>• Labeling</li> <li>• Surface and bulk homogeneity</li> <li>• Drop and vibration test</li> <li>• Seal integrity</li> <li>• Microbial barrier OR Whole package physical integrity</li> </ul>
PMMA plus polypropylene, polyimide, or PVDF	1	Medium	<ul style="list-style-type: none"> <li>• Dimensions</li> <li>• Surface and bulk homogeneity</li> <li>• Extractables<sup>5</sup></li> <li>• Cytotoxicity<sup>6</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Labeling</li> <li>• Seal integrity</li> <li>• Microbial barrier OR Whole package physical integrity</li> </ul>	<ul style="list-style-type: none"> <li>• Labeling</li> <li>• Surface and bulk homogeneity</li> <li>• Drop and vibration test</li> <li>• Seal integrity</li> <li>• Microbial barrier OR Whole package physical integrity</li> </ul>
Cross-linked polydimethyl-siloxane <sup>7</sup> alone or plus polypropylene, polyimide, PMMA, or PVDF	2	Low, Medium, High	<ul style="list-style-type: none"> <li>• Dimensions</li> <li>• Folding/Injection testing<sup>8</sup></li> <li>• Haptic pull test<sup>9</sup></li> </ul>		
		Medium	<ul style="list-style-type: none"> <li>• Surface and bulk homogeneity</li> <li>• Dioptric power</li> <li>• Imaging quality</li> <li>• Spectral transmission</li> <li>• Extractables<sup>5</sup></li> <li>• Cytotoxicity<sup>6</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Labeling</li> <li>• Seal integrity</li> <li>• Microbial barrier OR Whole package physical integrity</li> </ul>	<ul style="list-style-type: none"> <li>• Labeling</li> <li>• Surface and bulk homogeneity</li> <li>• Drop and vibration test</li> <li>• Seal integrity</li> <li>• Microbial barrier OR Whole package physical integrity</li> </ul>

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RI Material	No. of finished RI lots <sup>1</sup>	Dioptric power range <sup>2</sup>	Tests per study type (minimum 10 RIs per lot)		
			Product stability	Package integrity <sup>3</sup>	Shipping stability <sup>4</sup>
Any other combination of materials not listed above	3	Low Medium High	<ul style="list-style-type: none"> <li>• Dimensions</li> <li>• Dioptric power</li> <li>• Imaging quality</li> <li>• Folding/Injection testing (for foldable lenses)<sup>8</sup></li> <li>• Haptic pull test<sup>9</sup></li> </ul>		
		Medium (in addition)	<ul style="list-style-type: none"> <li>• Surface and bulk homogeneity</li> <li>• Compression force</li> <li>• Dynamic fatigue testing</li> <li>• Extractables<sup>5</sup></li> <li>• Cytotoxicity<sup>6</sup></li> <li>• Spectral transmission</li> <li>• Specific surface tests (if warranted)</li> </ul>	<ul style="list-style-type: none"> <li>• Labeling</li> <li>• Seal integrity</li> <li>• Microbial barrier</li> </ul> OR Whole package physical integrity	<ul style="list-style-type: none"> <li>• Labeling</li> <li>• Surface and bulk homogeneity</li> <li>• Drop and vibration test</li> <li>• Seal integrity</li> <li>• Microbial barrier</li> </ul> OR Whole package physical integrity

Notes:

- 1 Number of finished lots for product stability testing.
- 2 If characteristics such as dimensions, etc. are different depending on implant power, testing should be performed on different powers as indicated.
- 3 All package integrity testing should be performed on samples from the same finished lot(s). A minimum of three finished lots should be tested regardless of RI material.
- 4 Only one lot of medium power RIs is needed for shipping testing regardless of lens type.
- 5 For a description of a suitable extraction method, see Annex B of ISO/DIS 11979-6.
- 6 Cytotoxicity testing should be performed if an increase is seen in extractables content or if a new substance is present.
- 7 Sponsors may submit a rationale to support product stability testing on fewer than three lots for materials other than PMMA or cross-linked polydimethylsiloxane. The rationale should demonstrate that the material has a history of use in ocular implants, such as IOLs, that have been produced by more than one manufacturer.
- 8 For a description of folding/injection testing, see the section of this guidance entitled “Mechanical Properties and Test Methods.”
- 9 Applies only to RIs with haptics.

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**Annex E (informative) Recommended Postoperative Examination Schedule**

	<b>Preop</b>	<b>Op</b>	<b>Day 1</b>	<b>Week 1</b>	<b>Month 1</b>	<b>Month 3</b>	<b>Month 6</b>	<b>Month 12</b>	<b>Month 24</b>	<b>Month 36</b>
Distance UCVA	X		X	X	X	X	X	X	X	X
Distance BSCVA	X			X	X	X	X	X	X	X
Near UCVA	X			X <sup>2</sup>	X <sup>2</sup>	X <sup>1,2</sup>	X <sup>2</sup>	X	X	X
Near BSCVA	X			X <sup>2</sup>	X <sup>2</sup>	X <sup>1,2</sup>	X <sup>2</sup>	X	X	X
Manifest refraction	X	X <sup>3</sup>		X	X	X	X	X	X	X
Cycloplegic refraction	X							X	X	X
Axial length	X									
Intraocular pressure	X	X <sup>4</sup>	X	X	X	X	X	X	X	X
Slit lamp exam	X		X	X	X	X	X	X	X	X
Gonioscopic exam	X						X	X	X	X
Dilated fundus exam	X				X			X	X	X
Mesopic pupil size	X						X <sup>5</sup>			X
Pachymetry	X	X <sup>6</sup>					X			X
Keratometry <sup>7</sup>	X	X						X		X
Topography <sup>8</sup>	X				X		X			
Subject questionnaire	X						X	X	X	X
Contrast sensitivity	X					X <sup>9</sup>	X <sup>9</sup>			X
Specular microscopy	X					X <sup>9</sup>	X <sup>9</sup>	X	X	X

1 - for hyperopia protocols

2 - for presbyopia protocols

3 - for contact lens wearers

4 - post-surgery operative day IOP measurements should be considered if pupillary block is a possible complication

5 - should be performed at the same visit as contrast sensitivity testing

6 - if required for the surgical procedure

7 - to establish preoperative refractive stability for CL wearers and to demonstrate postoperative corneal stability where necessary

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8 - for devices that are intended to alter the cornea

9 - these tests may be performed at either the Month 3 or the Month 6 exam, but should be performed at the same exam for all subjects